

REMARKS

The application has been examined with respect to claims 9-12, 14-22, 24-26, 28, 30 and 35. Claims 10, 14, 16, 20, 22, 24, 26, 28 and 30 have been canceled. Claims 9, 11, 12, 15, 17-19, 21, 25 and 35 remain present in the application.

Claims 9, 12, 15, 17-19, 21, 25 and 35 have been amended as discussed in greater detail further below. No new matter has been introduced.

Claims 9, 11, 12, 15, 17-19, 21, 25 and 35 were rejected in the Office Action under reply. The Examiner's detailed comments in the Office Action are gratefully noted herein as being very helpful in clearly defining the issues to be discussed. The rejections and related items set forth in the Office Action are addressed by applicant as follows.

**I. Objection to the Disclosure
(Drawings) under 37 C.F.R. 1.84**

On page 3 of the Office Action, an objection has been made to the drawings for the informalities stated in PTO Form 948, which accompanied the Office Action. These informalities have been noted by applicant's counsel and will be attended to in due course upon an indication of allowable subject matter.

II. Objection to the Inventor's Oath/Declaration

On page 3 of the Office Action, an objection has been made to the inventor's oath/declaration as being inconsistent with the continuing data referred to in the specification. In particular, the Examiner has stated that the present declaration fails to refer to related prior application Serial No. 07/232,482 filed on August 17, 1988. However, the reason for the Examiner's objection is not understood by applicant's counsel.

It is counsel's understanding that, when filing a continuation or divisional application under 37 C.F.R. 1.60, it is only necessary to file a photocopy of the oath/declaration from the parent case. That has been done here. In particular, the present divisional was filed with a photocopy of the specification, claims and oath/declaration from 08/034,460, filed March 18, 1993, which was a copy of the specification, claims and oath/declaration from Serial No. 07/232,482, filed August 17, 1988. The inventor's declaration from Serial No. 07/232,482 refers to its parent, namely Serial No. 07/094,307, filed September 4, 1987. The declaration does not refer to its own serial number (07/232,482), because that number was not assigned until after the filing. Consequently, there does not appear to be impropriety in the oath/declaration filed in the present case. If the Examiner does not agree, applicant's counsel will be pleased to cooperate with any further suggestion the Examiner may have to clarify the record.

**III. Objection to the Specification
under 35 U.S.C. §112, First Paragraph**

The specification have been objected under 35. U.S.C. §112, first paragraph, as being unsupportive of the claim recital that the analogs are "free" of enzymatic activity associated with reactogenicity. The Examiner has specifically noted that the word "substantially" was previously recited in claims 12 and 22 to describe the lack of enzymatic activity, and that these claims were modified in the Preliminary Amendment of record to omit "substantially".

Claim 12 has now been amended to include the word "substantially". In addition, claims 9, 18, 19 and 35 have been modified to add "substantially" as a modifier of the term "free" which appears in these claims. Moreover, Claim 22 has been canceled. It is submitted that the objection has thus been overcome.

**IV. Rejection of Claims
under 35 U.S.C. §112, Second Paragraph**

On page 3 of the Office Action, Claims 9-12, 14-22, 24-26, 28, 30 and 35 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failure to particularly point out and distinctly claim the subject matter of the invention. In particular, claims 9, 17, 18, 19, 24 and 35 have been singled out as lacking antecedent basis for usage of the article "the" in certain places, and claims 10 and 19 (it is believed claim 20 was intended by the Examiner) have been cited for use of the language "major epitope known to be important in providing immunoprotection".

It is believed that the rejection has been overcome by the present amendment of the claims to delete the above-mentioned article where indicated in the Office Action as objectionable and to modify claim 17 by adopting the language suggested by the Examiner ("which includes an amino-terminus methionylvalyl sequence"). Claims 10 and 20 have been canceled.

**V. Rejection of Claims
under 35 U.S.C. §112, First Paragraph**

On page 5 of the Office Action, Claims 9-12, 14-26, 28, 30 and 35 have been rejected under 35 U.S.C. §112, first paragraph, as being based on a disclosure that purportedly enables only the arginine 9 to lysine analog for pertussis. It is noted herein by applicants' counsel that the rejection encompasses previously canceled claim 23, which is presumably an oversight. In brief, it is the Examiner's position that the disclosure is enabling only for claims limited to the arginine 9→lysine analog of pertussis toxin.

Applicant does not agree with the rejection or the Examiner's reasoning. The claim scope has already been narrowed considerably in the Preliminary Amendment of record in order to facilitate the allowance subject matter, especially in view of all the time lost since this application was first filed in 1987.

However, the Examiner does make the point that, for practical purposes, the arginine 9 position has been the only site within the valine 7 to proline 14 region proven to be effective for detoxification. With that in mind, the claims at issue have now been further amended to omit the reference to the valine 7 to proline 14 region, and to specify an arginine 9 substitution in every case.

While amendment falls short of the requirement to limit the mutation at arginine 9 to lysine only, it is hoped that the Examiner will permit some flexibility in this regard. True enough, applicant has exemplified only lysine as a substitute for arginine at this site. However, the amount of experimentation that might be necessary to find equivalents can hardly be regarded as unduly burdensome, or to rise to the level of a different invention. There are only a very limited number of amino acid residues that can substituted for arginine 9, besides lysine. Moreover, it is well established that patent claims are interpreted so as not to include inoperative species. Thus, to the extent that any substitutions at the arginine 9 site would not work, the claim does not encompass them anyway. With this mind, it is submitted that the claims meet the requirements of 35 U.S.C. §112, first paragraph, and should be favorably considered. Otherwise, there is a danger that attempts may be made to circumvent applicant's claims by effecting arbitrary substitutions falling outside the literal terms, even though it is applicant's intention to embrace obvious variations.

It should be noted that claims 15, 18, 25 and 35 already specify arginine 9 to lysine analogs and should be regarded as free of this rejection in any event.

To address other concerns raised by the Examiner in the Office Action, Claims 16 and 26, directed to bacterial species other than *B. pertussis*, and claims 28 and 30, directed to genetically engineered subunits of pertussis other than S1, have all been canceled. Additionally, claims 19, 21, 25 and 35 have been modified to omit the word "improved" as being nonessential to patentability.

VI. Rejection of Claims under 35 U.S.C. §103

Claims 9-12, 14-22, 24-26, 28, 30 and 35 have been rejected under 35 U.S.C. §103 as being unpatentable over the disclosure of U.S. Patent No. 4,883,761 (Keith et al.). The reference is relied on by the Examiner for its teachings regarding the "cloning and expression" of pertussis toxin subunits S1-S5. The reference is further relied on for its disclosure of the valine 7 to proline 14 region of pertussis S1 as a functional domain for catalytic activity by comparison with other related toxins, and the suggestion that such a region could be manipulated genetically for the purpose of eliminating untoward side effects (page 10 of the Office Action).

Applicant does not agree that the claimed invention would have been obvious from the disclosure of the Keith et al. patent. First, applicant takes issue with the Examiner's statement that the Keith et al. patent teaches the expression of the pertussis toxin genes. In point of fact, while the patentees were successful in cloning and sequencing these genes, they were not successful in expressing them (see column 22, lines 58-61). Indeed, the patent fails to disclose any proven means by which the genes could be recombinantly expressed for purposes such as genetic manipulation. Its value as prior art is therefore highly questionable.

Second, contrary to what is stated on page 10 of the Office Action, the Keith et al. patent does not teach that the valine 7 to proline 14 region is the functional domain for a catalytic activity. Instead, the patent states that the homologous region "may be part of functional domains for a catalytic activity in the subunits for all three toxins" (column 17, lines 46-47). This is hardly a definitive teaching of ADP-ribosylating activity. Moreover, it is not at all clear from the patent's disclosure that any meaningful conclusions in this regard can be drawn simply by comparing pertussis to other known toxins such as cholera and *E. coli* heat labile toxins, as the Examiner contends. For instance, Keith et al. state that:

"Two regions with significant homology to cholera and *E. coli* heat labile toxins were found (Table 4). They are tandemly located in analogous regions of all three toxins. However, the three amino acid differences found in these regions cannot be explained by single base

pair changes in the DNA. Furthermore, in most cases the homologous amino acids use quite different codons in pertussis toxin compared to cholera and heat labile *E. coli* toxins. This, together with the fact that no other significant homology in the primary structure could be found and that the amino acid sequences of the other subunits are completely different ... strongly suggests that pertussis toxin is not evolutionarily related to any of the other known bacterial toxins." (column 22, lines 47-62)

Other portions of the patent text, such as the following, make the picture even hazier and render it doubtful that the substitution for an individual amino acid in the valine 7 to proline 14 region will lead to a loss of enzymatic activity:

"It is proposed that the two enzymatically-active domains lie in two different regions of the protein, one at the amino-terminal half of the subunit for the acceptor substrate (Ni) binding and the other at the carboxy-terminal half of the subunit for the donor substrate (NAD+) binding." (column 22, lines 9-14)

The above teaching suggests, if anything, that genetic manipulation should be effected in both homologous domains of S1 shown in Table 4 (column 16) of the patent, not just one, in order to achieve detoxification.

In summary, the disclosure of Keith et al. would not have lead a skilled worker in this art to the present invention. It is therefore maintained by applicant that claims 9, 11, 12, 15, 17-19, 21, 25 and 35 are patentable over this reference under 35 U.S.C. §103.

In closing, it is submitted that claims 9, 11, 12, 15, 17-19, 21, 25 and 35 are patentable, and a favorable action is accordingly requested.

Respectfully submitted,



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